Henrietta N. Ukwu, M.D., F.A.C.P.
Vice President
Worldwide Regulatory Affairs
Vaccines/Biologics

December 4, 2000

Merck & Co., Inc.
UN-B121
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 7176
Fax 610 397 2962
E-Mail: henrietta_ukwa@merck.com

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

MERCK
Research Laboratories

RE: Docket No. 00D-1400
Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important vaccines on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many potential drug and vaccine candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

We commend the Food and Drug Administration for taking the initiative to provide sponsors with guidance for the conduct of reproductive toxicity studies for preventive vaccines and the use of pregnancy registries for preventive vaccines indicated for females of childbearing potential and pregnant women. We have reviewed the draft document in detail and offer the comments below for consideration as this Guidance evolves. As this Guidance lacks line numbers by which to refer to specific sentences, we present our comments in the order in which the topic appears in the draft Guidance. Also, since they are separate issues, we have chosen to segregate our comments on the preclinical reproductive toxicity study requirements from those on the establishment of pregnancy registries.

We have significant concerns regarding the relevance and design of developmental and reproductive toxicity studies for vaccines. Our general scientific concerns are followed by specific comments on individual sections of the Guidance.

1. General Comments

The generation of an immune response is based on a multifactorial sequential cascade of events, which is strictly controlled by the genetic makeup of the host. The unique characteristics of individual vaccines and the species-specificity of the corresponding immunologic responses, along with the sequence of reproductive and developmental toxicity

00D-1400 C1

timelines in different species, make characterization of a relevant model an extremely difficult task. It is our opinion that there is no consensus in the scientific community at this time as to the rational basis for the design and conduct of these types of studies. We appreciate that this draft guidance may act as a catalyst to stimulate discussion of these issues. To that end, we believe that it is critical that an expert panel be convened by CBER to discuss the issues; define whether such studies are warranted in the first place; and if so, define appropriate hypotheses, potential experimental designs and relevant animal models.

Any issuance of guidelines would be premature without guidance from experts in the design and production of vaccines, developmental toxicologists and clinical investigators. As is acknowledged in this draft guidance, there is a need for a flexible approach for each product. Nonetheless, a basic agreement is needed on what the relevant parameters for discussion should be, based on a common understanding of what information would be relevant and useful for the assessment of human risk.

While the ICH S5A guidance document "Detection of Toxicity to Reproduction for Medicinal Products" (59 FR 48746, September 22, 1994) provides useful general guidance, the unique characteristics inherent to biologicals/vaccines need to be addressed before this type of testing should be considered. If not, we may risk generation of irrelevant or uninterpretable data that could either provide a false sense of security or impede the development of vaccines for critical medical needs.

Merck recommendation: A scientific panel of experts from Academia, Industry and Government should be established before the final guidance is issued. A thorough public scientific discussion on the purpose and appropriateness of such studies is warranted.

2. Purpose of Guidance – Products Covered

In the second paragraph of the Introduction, this draft Guidance acknowledges that "CBER reviews a broad spectrum of investigational vaccines," and that "there are a number of vaccines in clinical development specifically for maternal immunization." However, it does not directly address how the Guidance will be applied to investigational vaccines versus those vaccines already licensed.

Merck recommendation: This Guidance should be prospectively applied to new vaccines, for which the natural history and epidemiology of the wild type disease suggest untoward effects on females of reproductive age, on embryogenesis, and/or on newborn normal development. Therefore, it should not be applied retrospectively to licensed vaccines; new combinations containing licensed vaccines intended for the same age groups as originally licensed; or labeling supplements for licensed vaccines that provide updated information on an existing indication. As stated on a recent EMEA/CPMP, "*Note for guidance on preclinical pharmacological and toxicological testing of vaccines*", documentation of clinical and/or epidemiological data on exposure to the infectious agent or related vaccines during pregnancy

should be sufficient to evaluate the risk[1]. We recommend that the text of the first paragraph of the Introduction be revised to read,

"The purpose of this document is to provide sponsors with guidance for the conduct of reproductive toxicity studies for preventive vaccines and to consider establishing pregnancy registries for preventive vaccines indicated for females of childbearing potential and pregnant individuals. *This guidance will be applied prospectively to investigational vaccines. It will not apply retrospectively to licensed vaccines, new combinations of licensed vaccines intended for the same indications, or to labeling supplements for licensed vaccines that provide updated information on an existing indication.* The recommendations set forth in this document pertain to the assessment of reproductive toxicity potential of preventive vaccines for infectious diseases."

3. Purpose of the Guidance – Populations Covered

This Guidance acknowledges that there are many different types of vaccines and that the reproductive toxicity studies needed for each vaccine must be evaluated on a case-by-case basis. However, the many vaccines already licensed or under development for children less than five years of age, by definition, should not be subject to this Guidance. It would be helpful if the Guidance could explicitly address the target population to which this Guidance applies.

Merck recommendation: The last sentence of the Introduction should be modified to read,

"This guidance is intended to outline general and specific considerations that should be taken into account in the assessment of the reproductive toxicity for preventive vaccines *indicated for adolescent and adult populations*."

4. Definitions – Vaccine

The draft guidance correctly identifies combinations of different types of antigens as a "combination vaccine." However, the remainder of the text of the guidance utilizes the term "vaccine" without respect to the type of vaccine. Therefore, it appears from the text as written that combination vaccines would be subject to the same requirements for reproductive toxicity as other vaccines. While this is understandable if any of the component antigens have not previously been licensed, many combination vaccine vaccines under development are composed of antigens that are already included in licensed vaccines.

Merck recommendation: Combination vaccines for which the individual components are licensed should not be subject to requirements for reproductive toxicity when included in a combination vaccine. An additional sentence should be added to the paragraph in which "vaccine" is defined as follows:

"For the purpose of this document a vaccine is a product, the administration of which is intended to elicit an immune response(s) that can prevent or lessen the severity of one or more infectious diseases. A vaccine may be a preparation of a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, live irradiated cells, crude fractions or purified immunogens,

[1] EMEA – CPMP: Note for Guidance on preclinical pharmacological and toxicological testing of vaccines. London, 17 December 1997, CPMP/SWP/465/95

including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as plasmid DNA vaccines), live vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above (Ref. 1). *Combination vaccines intended for the same age groups as those for which the component antigens are already licensed are not the subject of this guidance.*"

5. Design of Reproductive Toxicity Studies

In Section IV.B.1, Specific Considerations – Immunological Parameters, and in Section IV.B.6, Specific Considerations – Follow-up Period, a variety of immunological assays are listed as an integral part of the developmental reproductive toxicity studies. The immunological assays specified in the Guidance are proposed to serve two purposes:

1. Establish the relevance of the animal model used for the developmental toxicity studies with respect to immunogenicity, and
2. Determine the role of immunological factors in an observed toxicity (mechanistic studies).

a) Immunological Parameters. The generation of an immune response after administration of a vaccine is a complex multifactorial event. This is especially true when considering interspecies comparisons. It is not clear what factors would constitute an "appropriate" immune response in a species. There is a request in the draft guidance for extensive qualitative and quantitative characterization of the antibody response in the dam, fetus and neonates. Generation of an antibody response is only one of a number of factors which could potentially correlate with an adverse response in the fetus (others include the antigen, other vaccine components, various cytokines, maternal toxicity and cell mediated responses, all of which are dependent on the host genetic background of the host, each with its own specific timeline). It is not clear that detailed kinetics of antibody production would be of value as a routine component in reproductive developmental toxicity studies. This is especially true if a lack of reproductive toxicity of a vaccine is demonstrated in a species in which the antibody response was already documented in separate, non-reproductive studies.

b) Animal Model. It should be recognized that there are a limited number of animal models available for study of reproductive toxicity, especially when there is a requirement for postnatal assessment. In assessing the appropriateness of a potential model, consideration must be given to those species for which reliable background data and historical experience are available to characterize and estimate the frequency of fetal abnormalities in control animals. Any use of non-traditional species would require extensive validation beforehand. For those species which are commonly used in developmental toxicity studies (rats, mice and rabbits), there are also species-specific factors to consider. Postnatal studies in rabbits are not practical. Mice are particularly sensitive to stress and strain in response to test agents due to the aggressiveness of the dam. In mice, there are significant concerns when administering large doses by intramuscular routes, which may cause significant maternal toxicity.

c) Dose. It is not clear what a suitable dose and dose regimen would be for preclinical studies that would bracket the human clinical dose level(s) to be studied. Preclinical dose levels are

often based on the volume of the material administered. In theory, the elicited response could vary depending upon when, during development, the dose is administered. With drugs and chemicals, it is a common practice to increase the dose until a maternal toxic response is generated. With vaccines, there may be limits to the volumes that can be administered; moreover, the timing and magnitude of the response are variables that need to be considered, especially when episodic dosing is utilized. We would like further clarification of the rationale for a human dose equivalent (1:1) or a 15-fold margin on a mg/kg basis.

d) Schedule and Exposure Period. The relationship of dose to developmental timing is one of the most difficult aspects in the design of developmental studies. Vaccine studies would be particularly challenging, given the limited dose series and the potentially different responses associated with an initial dose, subsequent priming doses and a booster dose. When the various immunologic responses to antigen, antibody, cytokines and cell mediated responses are also taken into consideration, design issues become very intricate. Additionally, it is necessary to consider the specific development periods of premating, organogenesis, lactation and appropriate controls. When all parameters are considered, study designs become unreasonably large and complex.

e) Follow-up. As stated in the section on immunological parameters, in the absence of any toxicity, extensive characterization of an immune response in the pups is unwarranted. With regard to developmental landmarks and functional testing as stated in the ICH guidance, the best indicator of preweaning development is body-weight. Other landmarks of development are highly correlated with body-weight. Functional studies (generally interpreted as behavioral studies) are not commonly conducted in preweaning pups due to their limited repertoire of responses and difficulty in the quantitation of those responses. Functional assessments are generally carried out during the postweaning period.

Merck recommendation: Requirements for concurrent evaluation of the immune response in developmental and reproductive toxicity studies should be removed from the Guidance. The suggested evaluation of potential immunopathological effects (Section B.1) and immune parameters in the follow-up period (Section B.6) should be considered to be mechanistic studies, that would only be considered if toxicity is observed in the developmental toxicity study. It would be desirable for the Expert Panel to agree upon a single exposure paradigm, especially considering that women in early pregnancy would likely be exposed unknowingly to only one injection.

6. Formulations to be Evaluated

Section V of this Guidance, Vaccine Product Class, states that reproductive toxicity studies should be performed with the final formulation. It is not clear from the text of the draft Guidance whether the Guidance is specifying that preclinical reproductive toxicity studies be performed with the formulation that is to be used in the clinic, or whether all formulations to be evaluated in the clinic must also be evaluated in reproductive toxicity studies. Sponsors often conduct pivotal studies with what is intended to be the "final" formulation, only to subsequently optimize a formulation for the market. There is no need to routinely require that reproductive toxicity studies be repeated with modifications of formulations that may occur after the completion of pivotal trials. Under such circumstances, the need for additional

preclinical studies should not be presumed, but instead should be evaluated on a case-by-case basis.

Merck recommendation: The Guidance should clarify that preclinical reproductive toxicity studies be performed with clinical formulations and the need to repeat reproductive toxicity studies with subsequent formulations should be evaluated on a case-by-case basis in consultation with CBER. The text of this paragraph should be revised to read,

"Reproductive toxicity studies should be performed in advance for *a* clinical vaccine formulation used in studies that enroll pregnant women..... The decision to perform multiple reproductive toxicity studies for vaccine products falling into a similar or the same product class will be made on a case-by-case basis. *The applicability of preclinical studies conducted with earlier clinical formulations of the vaccine to the commercial formulation of the vaccine should also be made on a case-by-case basis.*"

7. Conclusions – Reproductive Toxicity Studies

We believe that this Guidance should not be finalized before a panel of experts evaluates the goals and purpose of the proposed studies. The wording should clearly specify that the proposed guidance applies to vaccines under development, which are intended for adolescent and adult populations. Reproductive toxicity studies if any, should be performed with a clinical formulation and the need for additional reproductive toxicity studies with different formulations should be evaluated on scientific grounds and on a case-by-case basis.

8. Establishment of Pregnancy Registries

Merck is considered an industry leader in the use of pregnancy registries for post-marketing surveillance and currently runs the only pregnancy registry for a vaccine. Our Pregnancy Registry Program for Varivax has been in operation for five years. Much information concerning the consequences of exposure to the vaccine has been collected, reassuring health care providers and consumers as to the safety of the product.

Since we have seen the tangible benefits of a pregnancy registry for a vaccine, Merck supports the FDA recommendation that pregnancy registries be established, on a case-by-case basis, for vaccines intended for use by women of childbearing potential and for pregnant women.

Merck recommendations:

- The need for pregnancy registries should be based on the 1) type of vaccine (live attenuated vs. inactivated); 2) known adverse effect(s) of the wild-type disease on the pregnant woman and the fetus; and 3) preclinical findings.

- Pregnancy registries should be encouraged, but not required, for products with suspected risk. For other products, sponsors should be able to selectively develop a pregnancy registry for products likely to be used in women of childbearing potential and pregnant women, and to collect information on pregnancy outcomes in order to inform health care providers. This is the same recommendation Merck previously submitted to Docket No. 99D-1541, in a letter dated September 14, 1999, in response to the draft guidance for industry entitled, "Establishing Pregnancy Registries" (64 *FR* 30041, June 4, 1999).

- In our experience, most exposures to vaccine during pregnancy are reported before the outcome of the pregnancy is known. This provides a less biased sample than the retrospectively reported cases commonly seen with adverse experience reporting. The establishment of a pregnancy registry may encourage health care providers to prospectively report exposures in pregnancy, which will result in better postmarketing data.

- FDA should define, "exposure during pregnancy" for vaccines. While, drug exposures during pregnancy are typically defined as any exposure to a product from the first day of the last menstrual period (LMP), the duration of viremia following live virus vaccination may be difficult to define. Therefore, vaccination occurring prior to the LMP may need to be included in the definition of "exposure during pregnancy."

9. Conclusions – Establishment of Pregnancy Registries

Merck supports FDA's recommendation that the establishment of pregnancy registries be considered on a case-by-case basis for the purpose of monitoring vaccinated pregnant women and their offspring to determine the risks, if any, associated with use of vaccines during pregnancy. We urge that the section titled, "Establishment of Pregnancy Registries," be revised in accordance with our suggestions.

We welcome the opportunity to comment on this Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

Henrietta Ukwu, M.D.
Vice President
Worldwide Regulatory Affairs
Vaccines/Biologics

Guidance for Industry

Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* of notice announcing the availability of the draft guidance. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1488, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm

For questions regarding the content of this draft document contact Marion F. Gruber, Ph.D., (301) 827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
August 2000

TABLE OF CONTENTS

Note: Page numbering may vary for documents distributed electronically.

GUIDANCE FOR INDUSTRY:[1]

Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications

I. INTRODUCTION

The purpose of this document is to provide sponsors with guidance for the conduct of reproductive toxicity studies for preventive vaccines and to consider establishing clinical pregnancy registries for preventive vaccines indicated for females of childbearing potential and pregnant individuals[2]. The recommendations set forth in this document pertain to the assessment of the reproductive toxicity potential of preventive vaccines for infectious diseases.

The Center for Biologics Evaluation and Research (CBER) reviews a broad spectrum of investigational vaccines for the prevention of infectious diseases indicated for immunization of adolescents and adults. Thus, the target population for vaccines often includes females in their reproductive years who may become pregnant during the time frame of vaccination. In addition, there are a number of vaccines in clinical development specifically intended for maternal immunization with the goal of preventing infectious disease in the vaccinee and/or young infant through passive antibody transfer from mother to fetus. There are special considerations in assessing the risks versus the benefits of immunization programs for pregnant women and/or females of childbearing potential that should be addressed during the pre-marketing phase of the product. In addition to potential adverse effects on the safety of the pregnant women, there may be concerns that the vaccine exerts adverse effects on normal fetal development and/or the development of an active immune response in infants born to mothers vaccinated during pregnancy.

In the past, during the pre-marketing phase there were no data collected regarding the vaccine's safety in pregnant women. In general, during clinical development of vaccines not intended for use during pregnancy, pregnant women are actively excluded from participation in clinical trials. In addition, if pregnancy occurs during a study, treatment is usually discontinued and the woman is dropped from the trial.

---

[1] This guidance has been prepared by the Maternal Immunization Working Group in the Center for Biologics Evaluation and Research at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the assessment of the reproductive toxicity potential of preventive vaccines for infectious diseases. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] This document does not address concerns regarding male reproductive toxicity and fertility studies.

However, as more females of child-bearing potential participate in clinical trials of investigational products and more preventive vaccines are being developed that are indicated for adolescents and adults, there is increasing concern for the unintentional exposure of an embryo/fetus before information is available regarding the potential risk versus benefit of the vaccine. In addition, following approval, vaccines may be recommended for use in pregnant women or there may be situations of inadvertent exposure of the pregnant woman and her fetus to the vaccine. In these situations, in the absence of clinical data it is difficult for the practitioner to make an informed risk assessment. Therefore, pre-clinical reproductive toxicity studies provide an important systematic approach and may frequently present the only data source upon which to base estimations of risk to the pregnant mother and/or the developing fetus. However, there is virtually no scientific literature on animal reproductive toxicity testing for vaccine products. This guidance is intended to outline general and specific considerations that should be taken into account in the assessment of reproductive toxicity for preventive vaccines.

II. DEFINITIONS

A. Vaccine

For the purpose of this document a vaccine is a product, the administration of which is intended to elicit an immune response(s) that can prevent and/or lessen the severity of one or more infectious diseases. A vaccine may be a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above (Ref. 1).

B. Reproductive Toxicology

Reproductive Toxicology is "the study of the occurrence, causes, manifestations, and sequelae of adverse effects of exogenous agents on reproduction" (Ref. 2).

C. Developmental Toxicity

Developmental toxicity is any adverse effect induced prior to attainment of adult life. This includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally (Ref. 3)

III. VACCINE TARGET POPULATION AND TIMING OF PRE-CLINICAL REPRODUCTIVE TOXICITY STUDIES

Reproductive toxicity studies should be conducted for vaccines indicated for adolescents and adults and for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women. However, there are currently differences in the timing of these studies to support inclusion of either target population in clinical trials.

Maternal immunization: Data from reproductive toxicity studies for products indicated specifically for immunization of pregnant women should be available prior to the initiation of any clinical trial enrolling pregnant women.

Females of childbearing potential: For vaccines indicated for females of childbearing potential, subjects may be included in clinical trials without reproductive toxicity studies, provided appropriate precautions are taken, such as pregnancy testing and use of birth control. For these products, data from reproductive toxicity studies should be included with the initial Biologics License Application submission, if they were not submitted earlier in the Investigational New Drug Application (IND).

The need for these data is supported by the following consideration: a) the target population for vaccines often includes women in their reproductive years who may become pregnant during the time frame of vaccination; b) clinicians are confronted with situations where immunization of pregnant women may be appropriate, e.g., when pregnant women are thought to be at higher risk from complications of a vaccine preventable disease (e.g. influenza); and c) vaccine labeling must have a statement about use during pregnancy (21 CFR 201.57 (f)(6)). For instance, without animal reproductive toxicology information, inactivated/recombinant vaccines would usually be pregnancy category C which does not assist the physician with regard to risk assessment in special clinical settings. Currently, males may be included in phase I, II, and III clinical trials in the absence of male fertility studies, although such studies may be recommended for certain products in the future.

IV. DESIGN OF REPRODUCTIVE TOXICITY STUDIES

A. General Considerations

Each vaccine should be evaluated on a case-by-case basis whereby the features of the product and its intended clinical use should be taken into account when determining the design of the reproductive toxicity study. Interpretation of the data derived from the reproductive toxicity study should include assessing whether any correlation exists between risks identified in animals with potential risks in humans.

1. Previous clinical experience

All available clinical experience in pregnant females should be considered for any potential application to the design of reproductive toxicity studies in animals. Clinical experience derived from immunization of pregnant women may be helpful in the evaluation of the potential for any adverse outcome on the viability and development of offspring. Such information may also aid in the design/monitoring of appropriate pre-clinical studies, and for product labeling.

However, clinical data that may have been obtained from a small number of pregnant women enrolled in non-IND studies, e.g., immunized with an investigational vaccine, will not replace the need for comprehensive animal reproductive toxicity studies.

2. Previous pre-clinical experience

All data generated from prior acute or repeat dose pre-clinical toxicity studies should be reviewed for their possible contribution to the interpretation of any adverse developmental effects that appear in the reproductive toxicology studies, i.e., fetal toxicity secondary to maternal toxicity.

3. Application of ICH guidance document S5A

CBER is recommending use of the ICH S5A guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products," as a point of reference to assist in the design of reproductive toxicity studies in order to assess the potential teratogenic effect of biological products in general (Ref. 3). However, while the ICH document provides initial guidance, it is important to note that the best way to design a reproductive toxicity study for a biological product is to allow for a flexible framework. Preventive vaccines present a diverse class of biological products including live attenuated, inactivated, recombinant, polynucleotide, polysaccharide, and protein antigens, vectored vaccines, conjugate vaccines, adjuvanted vaccines or they may consist of a combination of different vaccine antigens. Thus, it is evident that product specific issues frequently arise that may require the pre-clinical testing to be tailored to the vaccine product under consideration. Thus, the sponsor should establish an early dialogue with CBER to reach agreement on specific design issues and study endpoints prior to the conduct of the study.

B. Specific Considerations

1. Immunological parameters

The most important feature distinguishing a vaccine from drugs and other biological products is the immune response that the vaccine is intended to induce. Thus, in addition to evaluating the potential for adverse effects on the mother and the developing fetus caused by the inherent properties of the vaccine antigen and/or vaccine formulation; reproductive toxicity studies should be designed to also assess the vaccine induced immune response as well as the potential for vaccine induced immunopathologic effects (i.e., the development of antibodies cross-reacting with fetal tissues and auto-antibodies or other responses that may adversely affect the development of the fetus). The assessment should include a) the detection of antibody production in the pregnant animal, b) the antibody transfer from the pregnant female to the fetus through antibody measurements in the newborn, and c) the presence, persistence and effects of the antibody response in the newborn. Serum samples collected from pregnant animals, cord blood or fetal tissues as well as blood samples from newborn animals should be assessed for antibody specificity and kinetics. Such evaluation may also include an examination of fetal tissue for potential cross-reactivity with passively transferred antibodies induced by immunizing the pregnant animal with the vaccine product.

2. Animal model

It is recognized that animal models are not always available and/or that responses induced in an animal model may not always be predictive of the exact human response. However, when designing a reproductive toxicity study, efforts should be made to establish a relevant animal model. Furthermore, the sponsor should provide a rationale for either the choice of the animal model or the lack thereof. The reproductive toxicity study does not necessarily need to be conducted in the traditional species, i.e., rats and rabbits. There is also no specific request for the routine use of two species, i.e., one rodent and one non-rodent at this time. Ideally, the vaccine should elicit an immune response in the animals. The immunogenicity of the vaccine may be evaluated in pre-clinical trials in non-pregnant animals. In cases where lack of an appropriate animal model hinders the assessment of an immune response, reproductive toxicity studies are still useful in providing important information regarding the safety of the vaccine components/formulation in the pregnant animal and/or the developing fetus.

3. Dose

Reproductive toxicity studies should include a dose response that brackets the intended clinical dose level in order to a) assess the potential toxic effect(s) that a particular dose may have on the dam and on the conceptus, b) define a safe dose, and c) define the

dose capable of eliciting an immune response. The dosing regimen should include a full human dose equivalent (e.g., 1 human dose = 1 rabbit dose). A dose scaled down because of feasibility considerations should ordinarily still exceed the intended human adult dose by at least 15 fold on a mg/kg basis.

4. Schedule

The immunization interval and frequency of immunization(s) in a reproductive toxicity study should be based on the clinically proposed immunization interval. Thus, episodic dosing of pregnant animals is likely to be more relevant than daily dosing. Also, modifications to the dosing frequency may be necessary depending on the kinetics of the antibody response induced in the animal. In certain cases it may be necessary to also administer a priming dose to the female prior to conception to allow for an immune response to occur considering the short gestation periods of the most commonly used animal models, i.e. rabbits and rats.

5. Exposure period

An important area to evaluate is the potential adverse effect(s) of the vaccine on embryo-fetal development. Thus, it is recommended that the vaccine be administered during the period of organogenesis, that is, the female is exposed to the vaccine from implantation to birth. In addition, to evaluate effects on the pregnant/lactating female and on early post-natal development of the offspring the study should also include a follow-up period from birth to weaning. These studies are defined as stages C-E in the ICH S5A document.

6. Follow-up period

Reproductive toxicity studies should include an in-life phase, i.e., follow-up of the pups from birth to weaning, to assess the immune response induced by the vaccine including the evaluation of a) maternal antibody transfer to the offspring, b) magnitude and persistence of antibodies in the newborn pups, c) effects of antibodies in the newborn, i.e., the potential interaction with host tissues, and d) presence of antibody in milk. In addition to an assessment of the immunologic parameters, the follow-up period would also allow an evaluation of neonate adaption to extra-uterine life, i.e., postnatal development and growth as well as maternal behavior. For certain vaccines, there may be concerns that immunization of pregnant females may interfere with the ability of the offspring to mount an active immune response to either the same or a related vaccine antigen. Such concerns may need to be addressed on a case-by case basis in clinical immunogenicity studies in infants born to mothers that have been immunized with the vaccine during pregnancy.

7. Endpoints

In addition to an evaluation of the immunological parameters, the assessments may include maternal weight gain, clinical observations, implantation number, corpora lutea number, litter size, live fetuses, fetal and embryonic deaths, resorptions, pup weight, crown-rump length as well as incidence of external, visceral and skeletal malformations. Postnatal evaluations may include maternal-newborn relationship, neonate adaptation to extra-uterine life, pre-weaning development and growth, survival incidence, developmental landmarks and functional testing (Ref. 3). The evaluation of a given endpoint will depend on the features of the product.

V. VACCINE PRODUCT CLASS

Reproductive toxicity studies should be performed in advance for every final clinical vaccine formulation used in studies that enroll pregnant women. To avoid performing multiple reproductive toxicology studies during development, sponsors may find it advantageous to conduct Phase 1 and Phase 2 studies in non-pregnant subjects. Results from these studies can be used as the basis for advancing the most promising product(s) to studies that enroll pregnant women. The decision to perform multiple reproductive toxicity studies for vaccine products falling into a similar or the same product class (e.g., 9- versus 11-valent pneumococcal conjugate vaccine; multivalent versus monovalent Group B *Streptococcus* (GBS) vaccine products) will need to be made on a case-by case basis.

VI. ESTABLISHMENT OF PREGNANCY REGISTRIES

If the vaccine is administered to females of childbearing potential or is specifically indicated for immunization during pregnancy, the safety of that vaccine in human pregnancy may need to be further evaluated in a systematic manner under a Phase IV commitment. Alternatively, data on potential risks with the use of the vaccine in pregnant individuals may be obtained for already marketed products in order for the sponsor to update the product label. It is therefore recommended that pregnancy registries are established for the purpose of monitoring the post-licensure experiences from vaccinated pregnant women and their offspring to determine risks associated with use of the vaccine during pregnancy. The decision to conduct a pregnancy registry should be made on a case by case basis and may depend on several parameters such as the availability and extent of data derived from pre-clinical and clinical studies. The agency has also published for comment, guidance with regard to the design of pregnancy registries and suggested outcomes entitled "Draft Guidance for Industry: Establishing Pregnancy Registries"(Ref. 4).

VII. REFERENCES

1. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (January 1999)

2. Ecobichon, Donald. "Reproductive Toxicology" in CRC Handbook of Toxicology, Derelanko M. and Hollinger M, Eds., CRC Press, 1995

3. International Conference on Harmonization (ICH) Harmonized Tripartite Guideline "Detection of Toxicity to Reproduction for Medicinal Products, (59 FR 48746, September 22, 1994)

4. Draft Guidance for Industry: Establishing Pregnancy Registries (June 1999)

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: Docket No. 00D-1400
Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important vaccines on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many potential drug and vaccine candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

We commend the Food and Drug Administration for taking the initiative to provide sponsors with guidance for the conduct of reproductive toxicity studies for preventive vaccines and the use of pregnancy registries for preventive vaccines indicated for females of childbearing potential and pregnant women. We have reviewed the draft document in detail and offer the comments below for consideration as this Guidance evolves. As this Guidance lacks line numbers by which to refer to specific sentences, we present our comments in the order in which the topic appears in the draft Guidance. Also, since they are separate issues, we have chosen to segregate our comments on the preclinical reproductive toxicity study requirements from those on the establishment of pregnancy registries.

We have significant concerns regarding the relevance and design of developmental and reproductive toxicity studies for vaccines. Our general scientific concerns are followed by specific comments on individual sections of the Guidance.

1. General Comments

The generation of an immune response is based on a multifactorial sequential cascade of events, which is strictly controlled by the genetic makeup of the host. The species-specificity of the response along with the sequence of reproductive and developmental toxicity timelines in different species, makes characterization of a relevant model an extremely difficult task. It

is our opinion that at this time that there is no consensus in the scientific community as to the rational basis for the design and conduct of these types of studies. We appreciate that this draft guidance may act as a catalyst to stimulate discussion of these issues. To that end, we believe that it is critical that an expert panel needs to be convened by CBER to discuss the issues and define whether such studies are warranted in the first place; and if so, to define appropriate hypotheses, experimental designs and animal models.

Any issuance of guidelines would be premature without guidance from experts in the design and production of vaccines, developmental toxicologists and clinical investigators. As is acknowledged in this draft guidance, there is a need for a flexible approach for each product. Nonetheless, a basic agreement is needed on what the relevant parameters for discussion are should be based on a common understanding of what information would be relevant and useful for the assessment of human risk.

While the ICH S5A guidance document "Detection of Toxicity to Reproduction for Medicinal Products" (59 FR 48746, September 22, 1994) provides useful general guidance, the unique problems inherent with regards to biologicals/vaccines need to be addressed before this type of testing should be considered. If not, we may risk generation of inappropriate or uninterpretable data that will provide a false sense of security or which may impede the development of vaccines for critical medical needs.

Merck recommendation: A scientific panel of experts from the Academia, the Industry and the Government should be established before the final guidance is issued. A thorough public scientific discussion on the purpose and appropriateness of such studies is warranted.

2. Purpose of Guidance – Products Covered

In the second paragraph of the Introduction, this draft Guidance acknowledges that "CBER reviews a broad spectrum of investigational vaccines," and "there are a number of vaccines in clinical development specifically for maternal immunization." However, it does not directly address how the Guidance will be applied to investigational vaccines versus those vaccines already licensed.

Merck recommendation: This Guidance should be prospectively applied to new vaccines, for which the natural history and epidemiology of the wild type disease suggest untoward effects on females of reproductive age, on embryogenesis, and on newborn normal development. Therefore, it should not be applied retrospectively to licensed vaccines or to labeling supplements for licensed vaccines that provide updated information on an existing indication. As stated on a recent EMEA/CPMP, "*Note for guidance on preclinical pharmacological and toxicological testing of vaccines*", documentation on clinical and/or epidemiological data on exposure to the infectious agent or related vaccines during pregnancy should be sufficient to evaluate the risk[1]. We recommend that the text of the first paragraph of the Introduction should be revised to read,

[1] EMEA – CPMP: Note for Guidance on preclinical pharmacological and toxicological testing of vaccines. London, 17 December 1997, CPMP/SWP/465/95

"The purpose of this document is to provide sponsors with guidance for the conduct of reproductive toxicity studies for preventive vaccines and to consider establishing pregnancy registries for preventive vaccines indicated for females of childbearing potential and pregnant individuals. *This guidance will be applied prospectively to investigational vaccines. It will not apply retrospectively to licensed vaccines or to labeling supplements for licensed vaccines that provide updated information on an existing indication.* The recommendations set forth in this document pertain to the assessment of reproductive toxicity potential of preventive vaccines for infectious diseases."

3. Purpose of the Guidance – Populations Covered

This Guidance acknowledges that there are many different types of vaccines, and that the reproductive toxicity studies needed for each vaccine must be evaluated on a case-by-case basis. However, the many vaccines already licensed, or under development for children less than five years of age, by definition, should not be subject to this Guidance. It would be helpful if the Guidance could explicitly address the target population to which this Guidance applies.

Merck recommendation: The last sentence of the Introduction should be modified to read,

"This guidance is intended to outline general and specific considerations that should be taken into account in the assessment of the reproductive toxicity for preventive vaccines *indicated for adolescent and adult populations.*"

4. Definitions – Vaccine

The draft guidance correctly identifies combinations of different types of antigens as a "combination vaccine." However, the remainder of the text of the guidance utilizes the term "vaccine" without respect to the type of vaccine. Therefore, it appears from the text as written that combination vaccines would be subject to the same requirements for reproductive toxicity as other vaccines. While this is understandable if any of the component antigens have not previously been licensed, many combination vaccine vaccines under development are composed of antigens that are already included in licensed vaccines.

Merck recommendation: Combination vaccines for which the individual components are licensed should not be subject to requirements for reproductive toxicity when included in a combination vaccine. An additional sentence should be added to the paragraph in which "vaccine" is defined as follows:

"For the purpose of this document a vaccine is a product, the administration of which is intended to elicit an immune response(s) that can prevent or lessen the severity of one or more infectious diseases. A vaccine may be a preparation of a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, live irradiated cells, crude fractions or purified immunogens, including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as plasmid DNA vaccines), live vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above (Ref. 1). *Combination vaccines in which the component antigens are already licensed are not the subject of this guidance.*"

5. Design of Reproductive Toxicity Studies

In Section IV.B.1, Specific Considerations – Immunological Parameters, and in Section IV.B.6, Specific Considerations – Follow-up Period, a variety of immunological assays are listed as an integral part of the developmental reproductive toxicity studies. The immunological assays specified in the Guidance would serve two purposes:

1. Establish the relevance of the animal model used for the developmental toxicity studies with respect to immunogenicity, and
2. Determine the role of immunological factors in an observed toxicity (mechanistic studies).

a) Immunological Parameters. The generation of an immune response after administration of a vaccine is a complex multifactorial event. This is especially true when considering interspecies comparisons. It is not clear what factors would constitute an "appropriate" immune response in a species. There is a request in the draft guidance for extensive qualitative and quantitative characterization of the antibody response in the dam, fetus and neonates. Since generation of an antibody response is only one of a number of factors which could potentially result in a toxic response (others include the antigen, other vaccine components, various cytokines, maternal toxicity, cell mediated responses, all of which are dependent on the host genetic background of the host), each with its own specific timeline. It is not clear that detailed kinetics of antibody production would be of value as an assessment of developmental toxicity. This is especially true if there is a lack of toxicity of a vaccine in a species in which the antibody response was already documented in non-reproductive studies. The timing of dosing as it relates to specific developmental stages (as discussed below) also needs to be considered.

b) Animal Model. It should be recognized that there are a limited number of animal models available for study of reproductive toxicity, especially when there is a requirement for postnatal assessment. In assessing the appropriateness of a potential model, consideration must be given to those species for which reliable background data and experience are available. Any use of non-traditional species would require extensive validation. For those species, which are commonly used in developmental toxicity studies (rats, mice and rabbits), there are also species-specific factors to consider. Postnatal studies in rabbits are not practical. Mice are particularly sensitive to stress and strain in response to test agents due to the aggressiveness of the dam. In mice, there are significant concerns when administering large doses by intramuscular routes, which may cause significant maternal toxicity.

c) Dose. It is not clear what a suitable dose would be for preclinical studies that would bracket the human clinical dose level(s) to be studied. Preclinical dose levels are often based on the volume of the material administered. The response elicited may vary depending when, during development, the dose is administered. With drugs and chemicals, it is a common practice to increase the dose until a toxic response is generated. With vaccines, there may be limits to the amounts that can be administered, and the timing and magnitude of the response are variables that need to be considered, especially when episodic dosing is utilized. We would like further clarification in the rationale for a human dose equivalent (1:1) or a 15-fold margin on a mg/kg basis.

d) Schedule and Exposure Period. The relationship of dose to developmental timing is one of the most difficult aspects in the design of developmental studies. The need to dose in an episodic fashion and the potential different responses to an initial vs. subsequent priming doses vs. a booster dose for all the various responses to antigen, antibody, cytokines and cell mediated responses are very complex issues. Additionally, it is necessary to consider the specific development periods of premating, organogenesis, lactation and appropriate controls. When all parameters are considered, study designs become unreasonably large and complex.

e) Follow-up. As stated in the section on immunological parameters, extensive characterization of an immune response in the pups are unwarranted as it represents only one of a possible number of endpoints and in this absence of any toxicity, is not justified. In regards to developmental landmarks and functional testing as stated in the ICH guidance, the best indicator of preweaning development is body-weight. Other landmarks of development are highly correlated with body-weight. Functional studies (generally interpreted as behavioral studies) are not commonly conducted in preweaning pups due to their limited repertoire of responses and difficulty in the quantitation of those responses. Functional assessments are generally carried out during the postweaning period.

Merck recommendation: Requirements for concurrent evaluation of the immune response in developmental and reproductive toxicity studies should be removed from the Guidance. The suggested evaluation of potential immunopathological effects (Section B.1) and immune parameters in the follow-up period (Section B.6) should be considered to be mechanistic studies, that would only be considered after toxicity is observed in the developmental toxicity study.

6. Formulations to be Evaluated

Section V of this Guidance, Vaccine Product Class, states that reproductive toxicity studies should be performed with the final formulation. It is not clear from the text of the draft Guidance whether the Guidance is specifying that preclinical reproductive toxicity studies be performed with the formulation that is to be used in the clinic, or whether all formulations to be evaluated in the clinic must also be evaluated in reproductive toxicity studies. Sponsors often conduct pivotal studies with what is intended to be the "final" formulation, only to subsequently optimize a formulation for the market. There is no need to routinely require that reproductive toxicity studies be repeated with modifications of formulations that may occur after the completion of pivotal trials. Under such circumstances, the need for additional preclinical studies should not be presumed, but instead should be evaluated on a case-by-case basis.

Merck recommendation: The Guidance should clarify that preclinical reproductive toxicity studies be performed with clinical formulations and the need to repeat reproductive toxicity studies with subsequent formulations should be evaluated on a case-by-case basis in consultation with CBER. The text of this paragraph should be revised to read,

"Reproductive toxicity studies should be performed in advance for *a* clinical vaccine formulation used in studies that enroll pregnant women.....The decision to perform multiple reproductive toxicity studies for vaccine products falling into a similar or the same product class will be made on a case-by-

case basis. *The applicability of preclinical studies conducted with earlier clinical formulations of the vaccine to the commercial formulation of the vaccine should also be made on a case-by-case basis."*

7. Conclusions – Reproductive Toxicity Studies

We believe that this Guidance should not be finalized before a panel of experts evaluates the goals and purpose of the proposed studies. The wording should clearly specify that the proposed guidance applies to vaccines under development, which are intended for adolescent and adult populations. Reproductive toxicity studies if any, should be performed with a clinical formulation and the need for additional reproductive toxicity studies with different formulations should be evaluated on scientific grounds and on a case-by-case basis.

8. Establishment of Pregnancy Registries

Merck is considered an industry leader in the use of pregnancy registries for postmarketing surveillance and currently runs the only pregnancy registry for a vaccine. Our Pregnancy Registry Program has been in operation for five years. Much information concerning the consequences of exposure to the vaccine has been collected, reassuring health care providers and consumers as to the safety of the product.

Since we have seen the tangible benefits of a pregnancy registry for a vaccine, Merck supports the FDA recommendation that pregnancy registries be established, on a case-by-case basis, for vaccines intended for use by women of childbearing potential and for pregnant women.

Merck recommendations:

- The need for pregnancy registries should be based on the 1) type of vaccine (live attenuated vs. inactivated); 2) known effect of the wild-type disease on the pregnant woman and the fetus; and 3) preclinical findings.

- Pregnancy registries should be encouraged, but not required, for products with suspected risk. For other products, sponsors should be able to selectively develop a pregnancy registry for products likely to be used in women of childbearing potential and pregnant women, and to collect information on pregnancy outcomes in order to inform health care providers. This is the same recommendation Merck previously submitted to Docket No. 99D-1541, in a letter dated September 14, 1999, in response to the draft guidance for industry entitled, "Establishing Pregnancy Registries" (64 *FR* 30041, June 4, 1999).

- In our experience most exposures to vaccine during pregnancy are reported before the outcome of the pregnancy is known. This provides a less biased sample than the retrospectively reported cases commonly seen with adverse experience reporting. The establishment of a pregnancy registry may encourage health care providers to prospectively report exposures in pregnancy, which will result in better postmarketing data.

- FDA should define, "exposure during pregnancy" for vaccines. While, drug exposures during pregnancy are typically defined as any exposure to a product from the first day of the last menstrual period (LMP), the duration of viremia following vaccination may be

difficult to define. Therefore, vaccination occurring prior to the LMP may need to be included in the definition of "exposure during pregnancy."

9. Conclusions – Establishment of Pregnancy Registries

Merck supports FDA's recommendation that the establishment of pregnancy registries be considered on a case-by-case basis for the purpose of monitoring vaccinated pregnant women and their offspring to determine the risks, if any, associated with use of vaccines during pregnancy. We urge that the section titled, "Establishment of Pregnancy Registries," be revised in accordance with our suggestions.

We welcome the opportunity to comment on this Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

DISTRIBUTION LIST

Mark Cukierski
Linda Hostelly
Joanne Lahner
Michelle Kloss
Robert E. Silverman (MRL)
Tamra Goodrow
Hillel Cohen
Carlo Russo
Keith Chirgwin
Luc Kuykens
Manal Morsy
Harry Guess
Brian Ledwith
Paul Coplan
Kristine Shields
Lauren Hetrick
Bob Sharrar
WORF
Bethesda Central File (Receipt Copy)

Align top of FedEx PowerShip Label here.

BLUE BELL PRINT CENTER
MERCK & COMPANY, INC.
BUILDING 5 EAST, BLA-11
BLUE BELL PA 19422
(610)397-2704

SHIP DATE: 05DEC00
ACC# 180687319

ACTUAL WGT: 1 LBS MAN-WT

TO: DOCKETS MANAGEMENT BRANCH
FDA
HFA-305 RM. 1061
5630 FISHERS LANE
ROCKVILLE MD 20852

4206 6806 8930

FedEx

REF: 57834.7746.040

PRIORITY OVERNIGHT WED

CAD# 0088786 05DEC00

Deliver by:
06DEC00

TRK# 4206 6806 8930 Form 0201

IAD AA

20852 -MD-US 19 GAIA

153077-87 RIT 09/00

On Time®

These copies are
OFFICIAL FDA Copies
not desk copies